

REMARKS

Election

The Applicants affirm election of Group I with traverse. The Applicants request that the Examiner rejoin claim 100 in Group II if claims 97-99 are deemed patentable. Claim 100 depends on these claims and thus incorporates all their limitation. MPEP 821.04

Specification

The Applicants note that 1711 is crossed out in the specification. This was corrected in the preliminary amendment filed on November 28, 2003 where 1711 was replaced with 1701.

Rejection over prior art

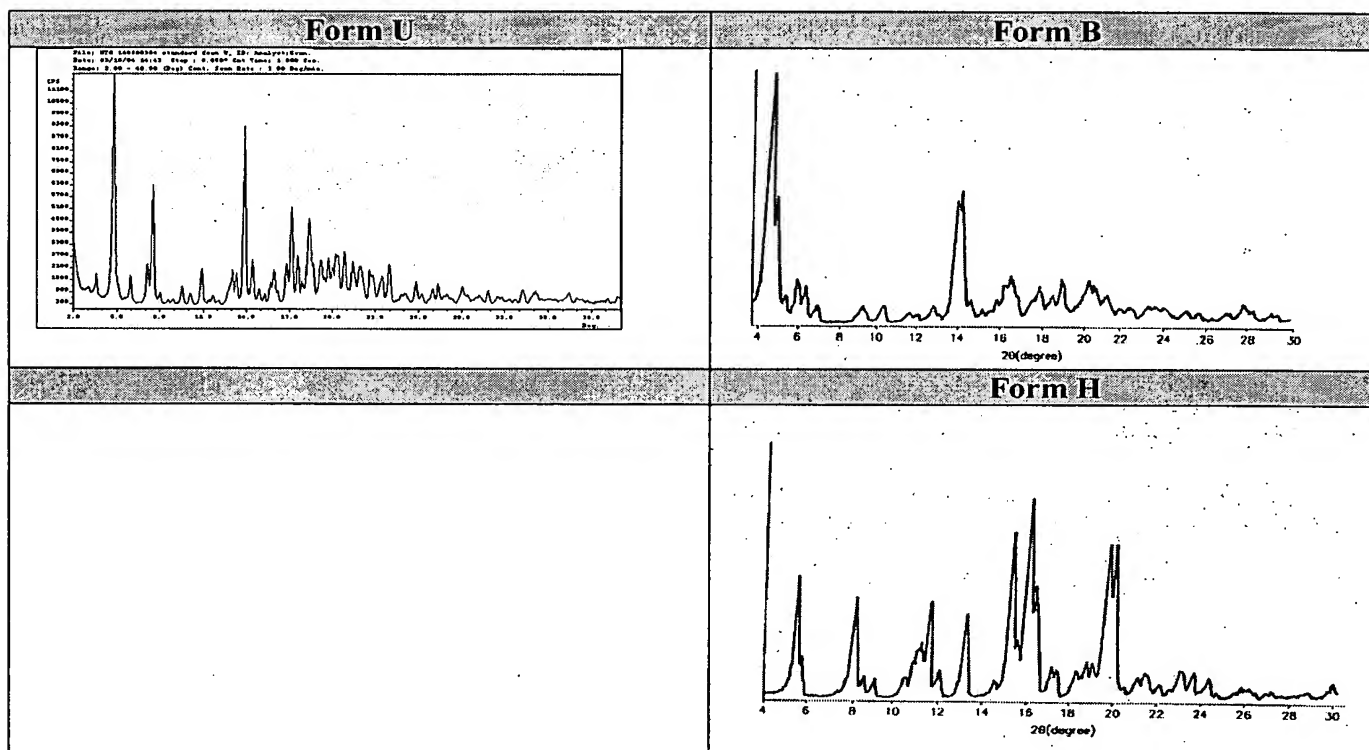
The Examiner rejects the claims under 102/103 in light of Sumikawa (US Pat 5,463,116).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Based on the present specification stating that the forms disclosed in Sumikawa, and the claimed Form U can be prepared from binary mixtures, the Office Action concludes that Sumikawa must have produced some Form U. The Office Action does not analyze the XRPD patterns of the products of Sumikawa to determine if Sumikawa's product contained Form U, and only states in conclusory fashion:

therefore anticipate the crystalline forms covered by the rejected claims. Alternatively, those of ordinary skill would expect that the crystals prepared by Sumikawa would invariably exhibit the XRPD patterns and FTIR spectra covered in the rejected claims, and therefore, the U-type crystalline form would be within the motivation of those of ordinary skill, and are thus prima facie obvious. See M.P.E.P. § 2112.01 ("Where the

As evident in the following side-by-side comparison, the Form U of the present invention has a substantially different XRD pattern than that for Forms B and H disclosed by Sumikawa:



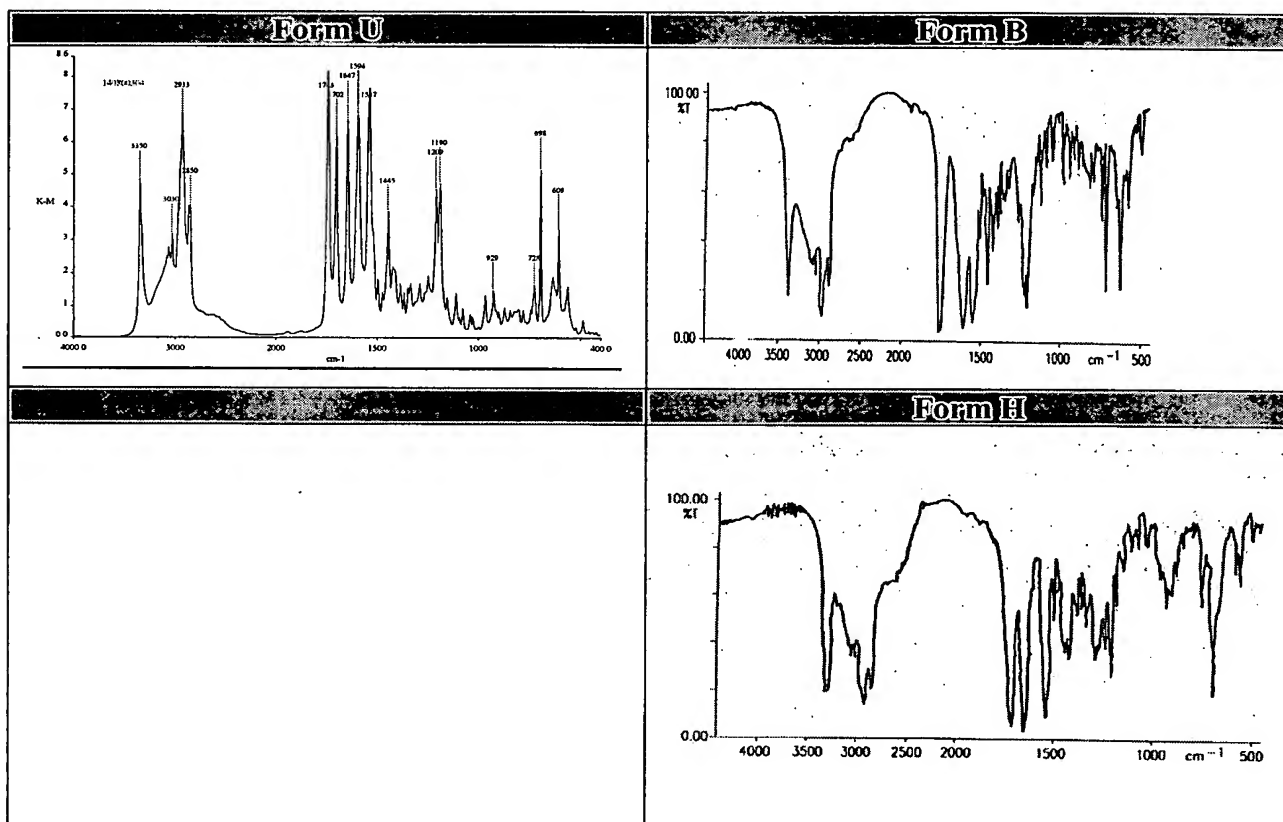
Form U is not detectable in the powder obtained for Forms B and H in Sumikawa. According to the present specification, and as claimed, Form U has the following XRDP peaks: 4.7, 7.4, 13.8 and 17.0 ± 0.2 degrees two theta. Figure 1 of Sumikawa, which discloses Form B, specifically lacks peaks, even small peaks, at 7.4 and 17.0 ± 0.2 degrees two theta. Figure 3, of Sumikawa, which discloses Form H, specifically lacks a peak, even a small one, at 13.8 ± 0.2 degrees two theta.

The use of XRPD to identify and distinguish polymorphs is the standard technique in the art:

X-ray powder diffraction is perhaps the “gold standard” for the qualitative determination of crystallinity. Not only can the presence of a crystalline phase be confirmed, but since each polymorph produces a unique diffraction pattern, the question of which polymorph crystallized can be addressed.

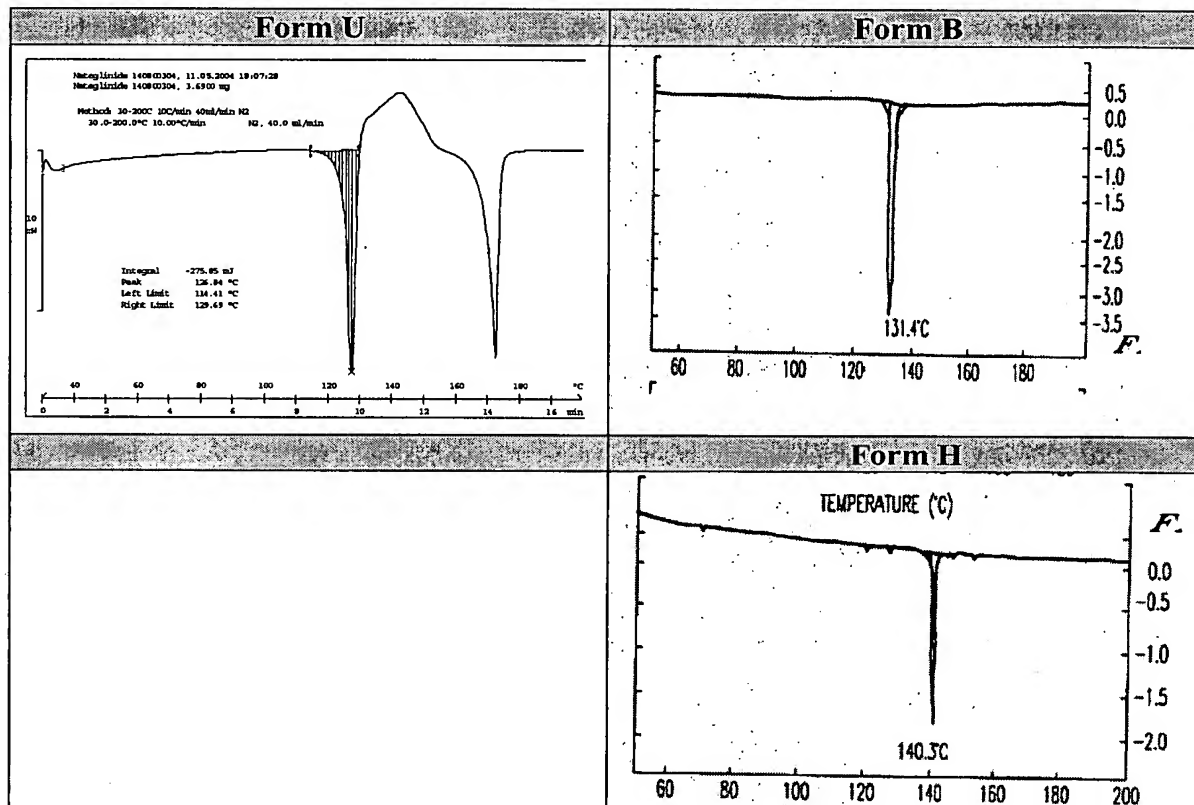
Brittain, H.G., *Polymorphism in Pharmaceutical Solids* p. 398-99 (Marcel Dekker 1999).
Thus, since the XRPD patterns disclosed in Sumikawa do not show presence of Form U as claimed in the present invention, Sumikawa cannot anticipate the claims of the present invention.

In addition to differences in XRD, Form U has different FTIR spectrum than those of Forms B and H:



The claimed FTIR spectrum peaks of 1291, 1646, 1701, and 3359 cm^{-1} for Form U differ from those provided for Form H in Sumikawa, mainly peaks at 1214, 1542, 1649 and 1714 cm^{-1} . Sumikawa does not provide specific peaks for Form B but as illustrated in the spectrum above, these forms have different FTIR spectrums as well.

The DSC thermograms of Form U is also substantially different that the those for Forms B and H:



Thus, Sumikawa cannot anticipate the claimed Form U of the present invention because Forms B and H are different and distinct from Form U.

Neither does Sumikawa render obvious the pending claims of the present invention. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaack*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

According to the Office Action:

anticipated by Sumikawa within the meaning of section 102, or alternatively, rendered *prima facie* obvious in view of Sumikawa within the meaning of section 103, since the reference invariably teaches the crystalline forms of nateglinide, or suggest the elements of the claimed crystalline forms with a reasonable expectation of success.

But Sumikawa does not teach or suggest nateglinide Form U or its existence, much less a process for its preparation with a reasonable expectation of success.

The unpredictable nature of polymorph generation precludes a *prima facie* case of obviousness. The literature is replete with references attesting to the unpredictability of polymorphs. "Perhaps the chief challenge in managing the phenomenon of multiple solid forms of drug is our inability to predict how many forms can be expected in any given case." Byrn, *et al.*, "Solid-State Pharmaceutical Chemistry," *Chem. Mater.* 6, 1148-1158 (1994). For example, only recently was a second polymorph for aspirin found despite being first synthesized in 1853. Wishweshwar, *et al.*, *J. Am. Chem. Soc.*, 127, 16802-16803 (2005). The process of crystallization is affected by many physical parameters, and this element of predictability has serious implications for solids design in crystal engineering. M. Caira, (Crystalline Polymorphism of Organic Compounds," *Topics in Current Chemistry*, vol. 198, 164-208 (1998). "There's no way to tell what a large floppy molecule can do in the solid state except by doing experiments." M. Rouhi, "The Right Stuff," *Chem. & Eng. News* 32-35 (2003). "Until that time [that computer programs are able to predict stable crystal forms] the development scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found." H.G. Brittain, "Polymorphism in Pharmaceutical Solids," p. 185 (Marcel Dekker 1999).

Therefore, the claimed Form U of the present invention is not obvious in view of the prior art due to unpredictable nature of polymorphism and polymorph generation.

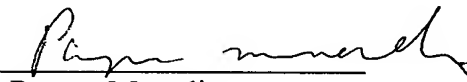
Double Patenting

The Applicants defer the provisional double patenting rejection until that time when there a claim that is deemed allowable.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the present application is in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. No fee is believed to be due for the submission of this response. Should any fees be required, please charge such fees to Kenyon & Kenyon, LLP Deposit Account No. 11-0600.

Respectfully submitted,

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